Model-Based Design of Novel Therapies for Heart Disease

Wednesday, January 24, 12:00 p.m. East Hall Room 1232

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Abstract
The mechanics of healing myocardial infarcts are a critical determinant of left ventricular function and the risk of an array of post-infarction complications including catastrophic rupture and progression to heart failure. Yet it has proven remarkably difficult to devise therapies to improve post-infarction prognosis by manipulating scar properties. This failure is largely due to the difficulty of predicting the outcome of interventions in such a complex system. Recently, computational models that harness rather than ignore this complexity have begun to provide novel insights into post-infarction mechanics and function, scar formation, and growth and remodeling of the heart, and to suggest new and unexpected therapeutic approaches. We used finite-element models to identify anisotropic reinforcement as a novel strategy to improve pump function of the heart following myocardial infarction, and validated this approach experimentally. We constructed an agent-based model of scar formation in the heart and showed that while chemokine gradients are a dominant regulator of collagen alignment in many healing wounds, mechanical stretch and pre-existing matrix orientation are more important in the heart. Using differential-equation-based models of collagen turnover and fibrosis signaling pathways, we explained the failure of prior attempts to modify infarct scar collagen content using matrix metalloproteinase (MMP) inhibitors, and proposed a novel strategy for achieving spatial control when modulating fibrosis in the heart. We are now beginning to predict growth and remodeling of the heart during the evolution of heart failure and in response to therapies such as cardiac resynchronization therapy (CRT). Similar approaches to atrial fibrillation in adults and congenital heart disease in children are also under development in the Cardiac Biomechanics Group at UVA. These models incorporate individual variability in hemodynamic responses, electrical and mechanical function, and anatomy, and predict outcomes and responses over the months and years relevant to clinical decision-making. Such models have the potential to provide customized design of therapies for individual patients with heart disease, but important regulatory and financial challenges must be addressed to achieve widespread impact.

Biography
Jeff Holmes is a Professor of Biomedical Engineering and Medicine at the University of Virginia. He obtained his B.S. in Biomedical Engineering from the Johns Hopkins University in 1989, his Ph.D. in Bioengineering from the University of California, San Diego in 1995, and his M.D. from the University of California, San Diego.
in 1998. His first faculty position was at Columbia University, where he helped found and build a new Biomedical Engineering department from 1999 to 2007. In 2007, Dr. Holmes moved to the University of Virginia, where he heads the Cardiac Biomechanics Group. His laboratory studies the interactions between mechanics, function, and growth and remodeling in the heart, using a combination of computational and experimental models. His research has been funded by the National Institutes of Health, the National Science Foundation, the American Heart Association, the Whitaker Foundation, the Coulter Foundation, the Hartwell Foundation, and the Allen Foundation. Dr. Holmes was awarded the Y.C. Fung Young Investigator Award in 2005, an American Heart Association Established Investigator Award in 2006, and is a Fellow of the American Heart Association, the American Institute for Medical and Biological Engineering (AIMBE), and the American Society of Mechanical Engineers. Dr. Holmes has taught a wide range of undergraduate and graduate courses including Computational BME, Fluid Biomechanics, Cardiac Mechanics, Soft Tissue Mechanics, Advanced Quantitative Physiology, Engineering Physiology, Biomedical Innovation, and Ethics for Biomedical Engineers. He currently serves as the founding Director of the Center for Engineering in Medicine at the University of Virginia.